UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/550,760 | 09/27/2005 | Anders Ljunggren | 133087.09001 | 3784 |

52286 7590 10/15/2010

Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183

| EXAMINER | |
|---|---|
| THOMAS, TIMOTHY P | |
| ART UNIT | PAPER NUMBER |
| 1628 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/15/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Advisory Action Before the Filing of an Appeal Brief | Application No. | Applicant(s) | |
|---|---|---|---|
| | *10/550,760* | LJUNGGREN ET AL. | |
| | Examiner | Art Unit | |
| | TIMOTHY P. THOMAS | 1628 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 04 October 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Timothy P Thomas/
Examiner, Art Unit 1628

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 11 and 17-20 under 35 U.S.C. 102(e) as being anticipated by Terashita, et al. (US 2006/0069133 A1).

Continuation of 11. does NOT place the application in condition for allowance because: The following rejections are maintained for the reasons of record:

Claims 11 and 17-20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Imura, et al. (US 2003/0187038 A1; priority claim 2000; cited in a prior Office Action)

Applicant argues that a declaration was previously submitted in which Anders Ljunggren, a co-inventor of the present application, states that he is unaware of any causative link between fibrinogen levels in a human and syndrome X or metabolic syndrome in a human and that the Imura reference fails to provide any data to support the position that syndome X is a fibrinogen-related disease; that the bare and unsupported statement in the Imura reference cannot be relied upon by one skilled in the art or the Office; that applicants' declaration has not been refuted with any teaching set forth in the Imura reference; accordingly one skilled in the art would not rely upon the Imura reference. This is not persuasive. The argument that Imura is not enabling was thoroughly addressed in the Final Office Action, mailed 7/2/2010. Applicant is refered to the record at Item 2, which already addressed this argument.

Although not required by the Office, as a courtesy to applicant, the Examiner discussed this rejection basis with his SPE, as requested by applicant.

Claims 11 and 17-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Imura et al. (US 2003/0187038; 2003; filed 2001; cited in a prior Office Action); and Yoneyama, et al. ("Cardiovascular Effects of L-158,809, a New Angiotensin Type 1 Receptor Antagonist, Assessed Using the Halothane-Anesthetized In Vivo Canine Model", 2002; Jpn. J. Pharmacol.; 89: 193-196; cited in a prior Office Action); and WHO ("Definition, Diagnosis and Classification of Diabetes mellitus and its Complications"; 1999; World Health Organization; Department of Noncommunicable Disease Surveillance. Geneva; pp. 1-59; accessed online on 12/9/2009 at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf); in view of Ortlepp et al. ("Inhibition of the rennin-angiotensin system ameliorates genetically determined hyperinsulinemia", 2002; European Journal of Pharmacology; 436: 145-150: IDS 3/25/2008 reference 1; cited in a prior Office Action).

Applicant argues that Imura is deficient, based on the Anders Ljunggren. This is not persuasive and has been addressed on the record; see Final Office Action, Item 2, mailed 7/2/2010.

Applicant argues that the Office fails to provide sufficient rebuttal evidence. This is not persuasive; the record indicates, in part, that at least each of following pieces of rebuttal evidence was discussed in the Final Office Action:

1) Data demonstrating reduction of fibrinogen levels is disclosed in Imura (see Experimental Example 1)

2) A search of PubMed for "fibrinogen" and "metabolic syndrome" on 7/1/2010 resulted in over 300 "hits", indicating there is much that is known in the art with respect to fibrinogen together with metabolic syndrome. Many of these references have dates that are prior to the earliest instant foreign priority date claimed, 4/3/2003.

3) Aso ("Plasminogen activator inhibitor (PAI)-1 in vascular inflammation and thrombosis"; 2007; Frontiers in Bioscience; 12: 2957-2966), which teaches impaired fibrinolysis may be associated with development of atherothrombotic cardiovascular disease (CVD) in metabolic syndrome or in type 2 diabetes; plasma plasminogen activator inhibitor (PAI)-1, a potent inhibitor of fibrinolysis, is elevated in a number of clinical situations that are associated with high incidence of CVD. Impaired fibrinolysis resulting from high plasma PAI-1 can lead to excessive fibrin accumulation within vessels, resulting in atherothrombosis; increased vascular expression of PAI-1 promotes neointima formation via accumulation of fibrin or fibrinogen as a result of inhibited clearance of platelet fibrin thrombi (abstract). This review article demonstrates that reduction in fibrinogen levels would be expected to provide a benefit in reduction of atherothrombotic cardiovascular disease in metabolic syndrome.

4) Carroll, et al. ("Plasma viscosity, fibrinogen and the metabolic syndrome: effect of obesity and cardiorespiratory fitness"; 2000; Blood Coagul. Fibrinolysis; 11(1): 71-8; PubMed abstract; PMID: 10691101) teaches the association between both plasma viscosity and fibrinogen concentration with a clustering of metabolic risk markers was examined; higher levels of hyperviscosity (2.08) was observed for subjects with metabolic syndrome when compared to those with no metabolic abnormalities; the results suggest that plasma viscosity is associated with increasing clustering of metabolic markers in middle-aged men of high socio-economic status. This article establishes that there is a link between fibrinogen levels and metabolic syndrome, leading to a reasonable expectation that reduction of fibrinogen (with reduction of plasma viscosity) will provide a benefit in treatment of metabolic syndrome.

5) The background section of Imura (see MPEP 2164.01, which indicates such information can support an enabling disclosure) teaches that plasma fibrinogen levels have been identified as an independent risk factor for cardiovascular diseases (paragraph 0002) and that ATII antagonistic activity are known to be therapeutic agents for circulatory system diseases such as hypertension, that prolonged hypotensive effect can be obtained by blocking the action of AII, which has strong vasoconstrictive activity (paragraph 0003). Reduction of fibrinogen as an independent risk factor would be expected to provide a benefit in metabolic syndrome. Reduction of blood pressure, which is often present in metabolic syndrome would provides a benefit for at least this component of metabolic syndrome, just based on the background disclosure.

6) The rejection is not based only on Imura. The record indicates that Ortlepp teaches the effects of angiotensin II receptor antagonist, irbesartan on the metabolic syndrome in an animal model, concluding long term treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist can ameliorate obesity and hyperinsulinemia in a genetically determined mouse model (abstract); initial administration of 0.0625 mg/g weight/day irbesartan, increasing to 0.2125mg/g at the age of 16 weeks was required to maintain an equipotent effect in reduction of blood pressure compared with captopril treatment (p. 146; Medication section); mice treated with Irbesartan had a body weight of 38.3 and a body weight gain and a gain of body weight of 4.3 g (Table 2); 0.0625mg/g x (38.3-4.3 g) corresponds to 2.0125 mg initial dosage; 0.2125mg/g x 38.3 g corresponds to 8.13875 g dosage at age 16 weeks. This reference provides evidence that an ATII antagonist provides multiple benefits in the treatment of metabolic syndrome, including weight loss, reduction of blood pressure and ameliorabion of hyperinsulinemia.

When the evidence is weighed, the conclusion is maintained that the Imura reference does not lack an enabling disclosure. Therefore, the rejection is maintained

Applicant argues the number of references is irrelevant. This is not persuasive. This search is an indicator of consideration of fibrinogen and metabolic syndrome taught together. Representative examples have been discussed.

Applicant argues that Aso is irrelevant, because it has a later publication date than the instant application date. For the purpuse of determining whether Imura is a non-enabling disclosure, based on the argument that Imura does not have data demonstrating a benefit for metabolic syndrome in humans, the reference is a valid indicator of whether Imura lacks enablement or is an enabling disclosure for treatment of metabolic syndrome with the claimed compound. The fact that Aso demonstrates that reduction in fibrinogen levels would be expected to provide a benefit in reduction of atherothrombic cardiovascular disease in metabolic syndrome, provides evidence for benefit in a patient subpopulation with metabolic syndrome.

Applicant argues that Cooke (taken to be a reference to the Carroll abstract) is misplaced, applicant quotes the statement that the comparable age-adjusted odds ratio for hyperfibrinogenaemia was non-significantly higher, without considering the other teachings relied on when this abstract was discussed. There are several comparisons made; the record indicates the association between both plasma viscosity and fibrinogen concentration with a clustering of metabolic risk markers was examined; higher levels of hyperviscosity (2.08) was observed for subjects with metabolic syndrome when compared to those with no metabolic abnormalities; the results suggest that plasma viscosity is associated with increasing clustering of metabolic markers in middle-aged men of high socio-economic status. This article establishes that there is a link between fibrinogen levels and metabolic syndrome, leading to a reasonable expectation that reduction of fibrinogen (with reduction of plasma viscosity) will provide a benefit in treatment of metabolic syndrome. This abstract is taken at face value for what it teaches.

Applicant argues that Ortlepp is different from the instant application because Ortlepp treats mice, but the instant application involves humans; the reference is argued to be irrelevent; an attempt is made to correlate the diagnostic criteria for humans, from WHO as being missing in the mouse model. This is not persuasive Ortlepp provides a teaching ofangiotensin II receptor antagonist, irbesartan on the metabolic syndrome in an animal model, concluding long term treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist can ameliorate obesity and hyperinsulinemia in a genetically determined mouse model. This model provides a reasonable expectation for similar benefits in humans. Even though the diagnostic criteria for humans and mice would be different, there would be a reasonable expectation of similar activity when compounds of the same class are utilized for treating humans with metabolic syndrome, that have the WHO levels for diagnosing metabolic syndrome.